

Report

Higher-Order Conditioning Is Impaired by Hippocampal Lesions

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Summary

Behavior in the real world is rarely motivated by primary conditioned stimuli that have been directly associated with potent unconditioned reinforcers. Instead, motivation and choice behavior are driven by complex chains of higher-order associations that are only indirectly linked to intrinsic reward and often exert their influence outside awareness. Second-order conditioning (SOC) [1] is a basic associative-learning mechanism whereby stimuli acquire motivational salience by proxy, in the absence of primary incentives [2, 3]. Memory-systems theories consider first-order conditioning (FOC) and SOC to be prime examples of hippocampal-independent nondeclarative memory [4, 5]. Accordingly, neurobiological models of SOC focus almost exclusively on nondeclarative neural systems that support motivational salience and reward value. Transfer of value from a conditioned stimulus to a neutral stimulus is thought to require the basolateral amygdala [6, 7] and the ventral striatum [2, 3], but not the hippocampus. We developed a new paradigm to measure appetitive SOC of tones in rats. Hippocampal lesions severely impaired both acquisition and expression of SOC despite normal FOC. Unlike controls, rats with hippocampal lesions could not discriminate between positive and negative secondary conditioned tones, although they exhibited general familiarity with previously presented tones compared with new tones. Importantly, normal rats' behavior, in contrast to that of hippocampal groups, also revealed different confidence levels as indexed by effort, a central characteristic of hippocampal relational memory. The results indicate, contrary to current systems models, that representations of intrinsic relationships between reward value, stimulus identity, and motivation require hippocampal mediation when these relationships are of a higher order.

Results and Discussion

We developed a new paradigm to test hedonic second-order conditioning (SOC) in rats by using auditory conditioned stimuli (see [Table S4](#) available online) that predicted whether water would be available in a neighboring chamber. The paradigm also allowed insight into rats' "confidence" in making response choices [8]. In this task (see [Figure 1](#), [Experimental Procedures](#), and [Supplemental Experimental Procedures](#)), rats acquired first-order conditioning (FOC) by using a two-

tone discrimination procedure signifying the availability of water in the opposite side of a test chamber. The positive (CS+) and negative (CS−) conditioned stimuli were then paired with SOC stimuli (SO+, SO−), followed by testing of both FOC and SOC. In three different experiments, we tested either retrograde (experiments 1a and 1b) or anterograde (experiment 2) memory following surgical intervention by using either multiple (experiment 1a) or single (experiments 1b and 2) secondary tones. Following Fortin et al. [8], multiple SOs were used in experiment 1a to allow the use of barriers of different heights as a challenge to approach the reward, indexing the rats' confidence in their memory and response choice. The use of multiple SOs also allowed us to be certain that rats developed genuine SOC rather than demonstrate generalization between the CS and a single SO.

On average, the lesions destroyed about 73% of the hippocampus, including 84% dorsal and 55% of ventral hippocampus ([Figure 2](#); [Figure S1](#); [Table S1](#); [Supplemental Results](#)).

Experiment 1a

As is evident from [Figure 3A](#), the hippocampal and sham-surgery control groups equally and successfully discriminated the positive (rewarded) and negative (nonrewarded) primary conditioned stimuli during FOC ($F[1,20] = 257.44$, $p < 0.001$; $\eta^2 = 0.93$) with no group (hippocampal versus control) difference ($F[1,20] = 0.2$, $p > 0.1$) or group \times tone-type (positive versus negative) interaction ($F[1,20] = 0.54$, $p > 0.1$) ([Figure 3A](#); [Figure S2](#)). This finding is consistent with the literature on FOC and the hippocampus. By contrast, only the control rats discriminated between the SO conditioned tones ([Figure 3B](#); [Figure S3](#)). There were significant effects of tone type ($F[2,40] = 37.95$, $p < 0.001$; $\eta^2 = 0.66$), barrier height ($F[4,80] = 101.01$, $p < 0.001$; $\eta^2 = 0.84$), and surgery ($F[1,20] = 5.45$, $p < 0.05$; $\eta^2 = 0.21$) reflecting overall shorter latencies for SO+ stimuli, longer latencies for higher barriers, and overall longer latencies for hippocampal rats. Importantly, there was a significant group \times tone-type interaction ($F[2,40] = 23.20$, $p < 0.001$; $\eta^2 = 0.54$). There were no group \times barrier or tone-type \times barrier interactions ($F[4,80] = 0.23$, $p > 0.1$; $F[8,160] = 0.64$, $p > 0.1$; respectively). Finally, there was a significant triple interaction of group \times tone type \times barrier ($F[8,160] = 2.3$, $p < 0.05$; $\eta^2 = 0.11$). Planned contrasts showed that, overall, latencies to run in response to SO+ tones were significantly shorter than to SO− tones ($F[1,20] = 69.92$, $p < 0.001$; $\eta^2 = 0.78$) and New tones ($F[1,20] = 50.33$, $p < 0.001$; $\eta^2 = 0.72$), with no difference between SO− and New tones ($F[1,20] = 0.99$, $p > 0.1$). The surgery \times tone-type interaction reflects shorter latencies in controls for SO+ versus SO− tones ($F[1,20] = 61.19$, $p < 0.001$; $\eta^2 = 0.75$), for SO+ versus New tones ($F[1,20] = 25.28$, $p < 0.001$; $\eta^2 = 0.56$), and for New versus SO− tones ($F[1,20] = 5.37$, $p < 0.05$; $\eta^2 = 0.21$). These interactions show that, unlike rats with hippocampal lesions, controls clearly differentiated between SO+ and SO− tones and between conditioned and new tones. The three-way interaction reflected a smaller effect of barrier height on latencies for SO+ stimuli in the control group with a more moderate linear increase ($F[1,20] = 11.25$, $p < 0.01$; $\eta^2 = 0.36$) and a flatter quadratic increase ($F[1,20] = 4.42$, $p < 0.05$; $\eta^2 = 0.18$) effects with higher barriers ([Figure 3B](#)). Thus, increasing barrier heights had the same

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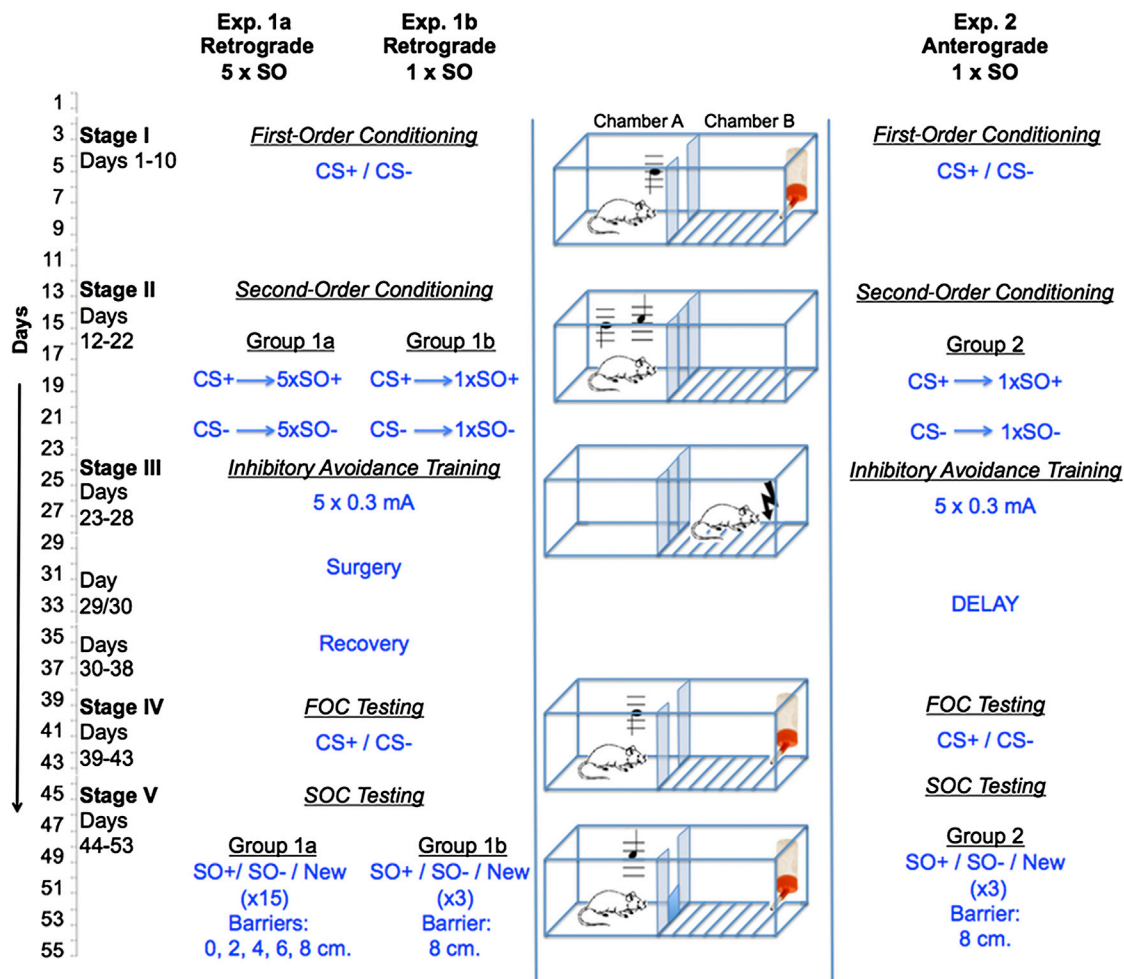


Figure 1. Design and Timeline of First- and Second-Order Conditioning and Testing for the Three Groups

Rats in experiment 2 had the surgical procedure 2 weeks prior to the beginning of stage I, allowing recovery time and water deprivation schedule before stage I. These rats had a delay of 10 days between stage III and stage IV in order to match the delay in experiment 1a and b.

slowing effect on hippocampal rats' latencies, regardless of tone type. By contrast, controls differentially responded to increased barrier heights, in a manner consistent with greater reliance on the information derived from the secondary associations. They slowed down most when more exertion, and therefore greater confidence in memory content, was needed to gain access to the water (cf. ROC, Figure S3E). The idea that the hippocampus is preferentially involved in representing high-confidence memory decisions is consistent with dual-process models, as well as several current single-process models [9, 10]. In apparent contradiction to dual-process models, hippocampal rats showed no evidence of familiarity (e.g., longer latencies for SO-, cf. ROC Figure S3E). Note, however, that in experiment 1a there were 15 relatively similar tones to be discriminated. Reliance on familiarity alone is unlikely to support such a difficult discrimination. In experiments 1b and 2, where only three tones needed to be discriminated, hippocampal rats displayed familiarity-based performance (see below).

A secondary ANOVA excluding the new stimuli revealed almost identical effects in that only control rats discriminated between SO tones. There were significant effects of tone type ($F[1,20] = 69.92$, $p < 0.001$; $\eta^2 = 0.78$), reflecting overall

shorter latencies for SO+ stimuli; significant barrier height effects ($F[4,80] = 66.63$, $p < 0.001$; $\eta^2 = 0.77$), reflecting linear ($F[1,20] = 135.5$, $p < 0.001$; $\eta^2 = 0.87$) and quadratic ($F[1,20] = 32.5$, $p < 0.001$; $\eta^2 = 0.62$) latency increases; and a significant effect of surgery ($F[1,20] = 4.74$, $p < 0.05$; $\eta^2 = 0.19$), reflecting overall slower responding for hippocampal rats. Importantly, there was a significant group \times tone-type interaction ($F[1,20] = 61.19$, $p < 0.001$; $\eta^2 = 0.75$), no group \times barrier or tone-type \times barrier interactions ($F[4,80] = 0.44$, $p > 0.1$; $F(4,80) = 1.1$, $p > 0.1$; respectively), but there was a significant triple interaction of group \times tone-type \times barrier ($F[4,80] = 3.23$, $p < 0.05$; $\eta^2 = 0.14$). This was further examined comparing SO+ and SO- directly and individually at different barrier heights. These analyses revealed significant shorter latencies for SO+ versus SO- in sham rats only for barrier heights 0 cm ($t(9) = -3.3$; $p < 0.01$), 2 cm ($t(9) = -4.5$; $p < 0.01$), 4 cm ($t(9) = -2.4$; $p < 0.05$), 6 cm ($t(9) = -6.9$; $p < 0.001$), and 8 cm ($t(9) = -4.64$; $p < 0.001$).

Experiment 1b

An obvious alternative account for the differential effects of hippocampal lesions is that rats had to learn to discriminate only two FOC stimuli but ten SOC stimuli, potentially making

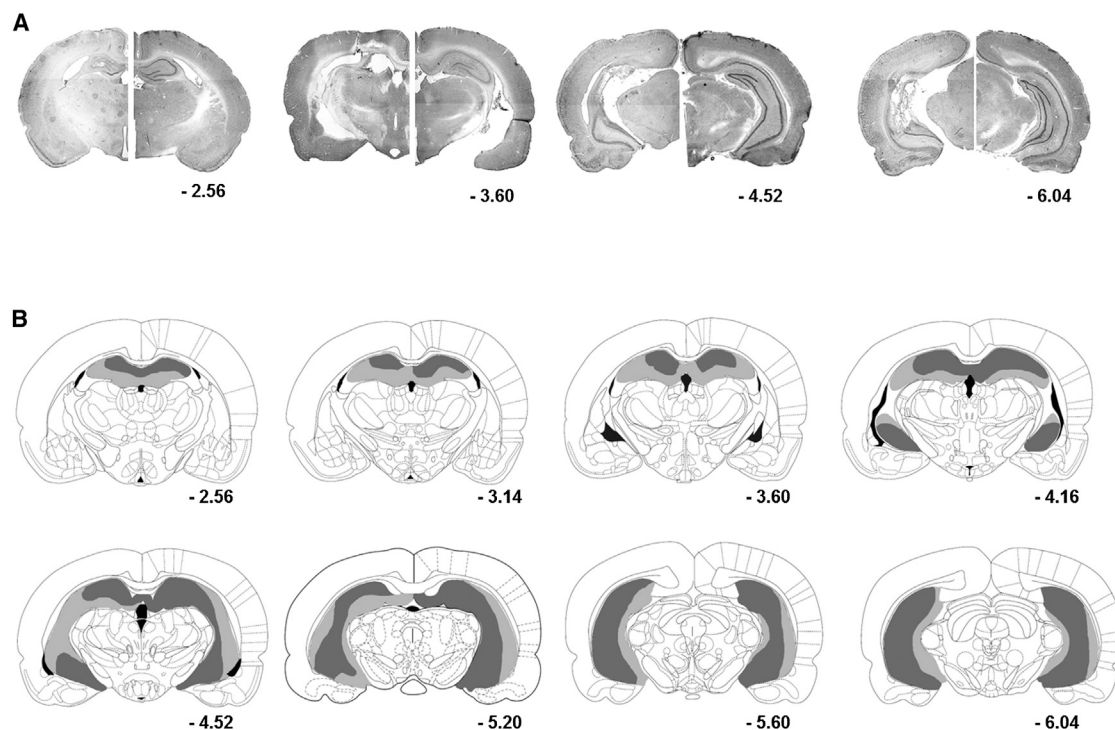


Figure 2. Extents of Hippocampal Lesions

(A) Example of representative hippocampal lesion (left hemisphere) and sham-operated control (right hemisphere) brain sections.

(B) Minimum (light gray) and maximum (dark gray + light gray) hippocampal lesion throughout the hippocampus in experiment 1a. Anterior to posterior stereotaxic coordinates of the coronal sections are relative to bregma.

the difference between the tasks simply a matter of difficulty. We therefore conducted a second experiment with only two SOC stimuli. Because of the small number of SOC stimuli, we decided to minimize low confidence responses and used only the highest confidence 8 cm barrier (see Experiment 2, [Supplemental Experimental Procedures](#) for fuller account). The differential effects of hippocampal lesions on FOC and SOC were replicated. Hippocampal and control rats equally and successfully discriminated positive and negative primary conditioned stimuli ($F[1,19] = 44.87$, $p < 0.001$; $\eta^2 = 0.70$) with no group difference ($F[1,19] = 2.22$, $p > 0.1$; $\eta^2 = 0.1$) or group \times tone-type interaction ($F[1,19] = 1.41$, $p > 0.1$; $\eta^2 = 0.07$) ([Figure 3A](#); [Figure S2](#)). In contrast, rats with hippocampal lesions did not express SOC even when only one SO stimulus was paired with each CS ([Figure 3C](#); [Figure S3](#)). There were significant effects of tone type ($F[2,38] = 49.21$, $p < 0.001$; $\eta^2 = 0.72$), as well as significant group \times tone-type interactions ($F[2,38] = 10.83$, $p < 0.001$; $\eta^2 = 0.36$) in the absence of group main effects ($F[1,19] = 0.21$, $p > 0.1$). Planned contrasts examining the significant differences and interactions in these analyses showed an overall effect such that SO+ latencies were shorter than SO- ($F[1,19] = 41.98$, $p < 0.001$; $\eta^2 = 0.69$) and New tones ($F[1,19] = 107.89$, $p < 0.001$; $\eta^2 = 0.85$) and the SO- latencies were shorter than New ($F[1,19] = 11.03$, $p < 0.01$; $\eta^2 = 0.37$). The group by tone-type interaction reflected hippocampal rats' shorter latencies for SO- compared with New ($F[1,19] = 4.79$, $p < 0.05$; $\eta^2 = 0.20$) and compared with SO+ ($F[1,19] = 23.82$, $p < 0.001$; $\eta^2 = 0.56$) and group by SO+ versus New latencies interaction ($F[1,19] = 5.70$, $p < 0.05$; $\eta^2 = 0.23$). Thus, even when equated for number of stimuli, FOC and SOC show differential sensitivity to hippocampal damage.

Experiment 2

Experiments 1a and 1b clearly demonstrated that hippocampal lesions preclude the expression of previously acquired SOC. In experiment 2, we asked whether SOC could be acquired independently of the hippocampus by using alternative pathways. Accordingly, in Experiment 2, we assessed the effects of hippocampal lesions on acquiring FOC and SOC. As in Experiment 1b, each CS was paired with a single SO tone and only the 8 cm barrier was used. Hippocampal and control groups equally and successfully discriminated positive and negative primary conditioned stimuli during FOC ($F[1,17] = 302.32$, $p < 0.001$; $\eta^2 = 0.95$) with no group difference ($F[1,17] = 2.14$, $p > 0.1$; $\eta^2 = 0.1$) or group \times tone-type interaction ($F[1,17] = 1.15$, $p > 0.1$; $\eta^2 = 0.06$) ([Figure 4A](#); [Figure S4](#)). By contrast, rats with hippocampal lesions were impaired in forming second-order associations ([Figure 4B](#); [Figure S4](#)). The SOC yielded a significant effects of tone type ($F[2,34] = 40.05$, $p < 0.001$; $\eta^2 = 0.70$) and a significant group \times tone-type interaction ($F[2,34] = 13.01$, $p < 0.001$; $\eta^2 = 0.43$). The overall group main effect was not significant ($F[1,17] = 0.22$, $p > 0.1$). Planned contrasts examining the significant differences and interactions in these analyses showed an overall effect such that SO+ latencies were shorter than SO- ($F[1,17] = 22.34$, $p < 0.001$; $\eta^2 = 0.57$) and New tones ($F[1,17] = 75.61$, $p < 0.001$; $\eta^2 = 0.82$) and the SO- latencies were shorter than New ($F[1,17] = 18.73$, $p < 0.001$; $\eta^2 = 0.52$). The tone by surgery interaction reflected hippocampal rats' shorter latencies for SO- compared with New ($F[1,17] = 27.98$, $p < 0.001$; $\eta^2 = 0.62$) and compared with SO+ ($F[1,17] = 11.99$, $p < 0.01$; $\eta^2 = 0.41$) no group by SO+ versus New latencies interaction ($p > 0.1$).

The findings from this study demonstrate for the first time that the hippocampus is critical for the acquisition and retrieval

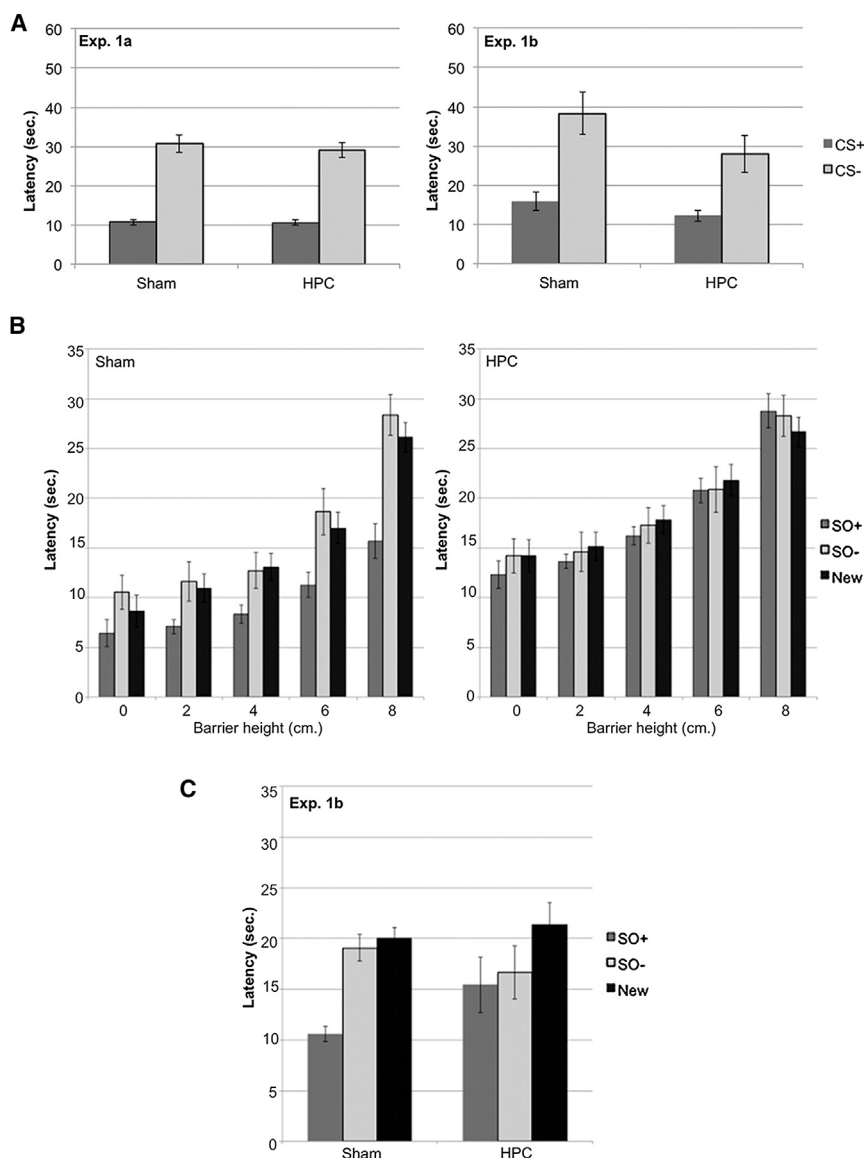


Figure 3. Response Latencies in Experiments 1a and 1b

(A) Latency to run for primary conditioned stimuli (CS+ versus CS-) during FOC testing (experiment 1a left, experiment 1b right).

(B) Latency to run across different barrier heights following presentation of SO stimuli and new stimuli during SOC testing in experiment 1a.

(C) Latency to run across the 8 cm barrier in experiment 1b for SO+, SO-, and New stimuli. Error bars are SEM.

updating of the reward value of the primary conditioned stimulus is mediated by the striatum, while the hippocampus mediates the flexible generalization of reward to previously associated stimuli [12, 13]. Notably, it is predicted that value transfer in SOC would not require the hippocampus [13] because the pairing phase occurs after value learning of one of the stimuli. The basolateral amygdala through its connections with the striatum should be sufficient to mediate value transfer under these conditions [13]. We discovered that the hippocampus, in fact, is required for intrinsic transfer of value; hippocampal lesions prevented the creation, and retention, of secondary associations that reflect the transfer of value from primary conditional stimuli to novel stimuli or between stimuli and internal hedonic states [2]. Interestingly, damage to basolateral amygdala has no effect on sensory preconditioning [13, 14] but profoundly impairs SOC [2, 3], suggesting that the latter is sensitive both to motivational salience and representational complexity of the stimuli.

The results of the three experiments reveal important characteristics of hippocampal processing during SOC. In

of higher-order associations in appetitive conditioning. Current models of conditioning have focused primarily on extra-hippocampal brain systems that contribute to representations and associative learning of reward value and motivation. These include the basolateral amygdala nuclei (BLA) for mediation of affective value; orbitofrontal cortex, thought to represent outcome expectancies that facilitate reward associative learning; and, in particular, the nucleus accumbens that is required for acquisition of conditioned appetitive responses [2, 3]. The hippocampus typically is considered important for forming relationships between stimuli that are not uniquely or directly associated with primary reinforcement, as in contextual fear conditioning where an aversive response is related to a constellation of background stimuli or for bridging long temporal gaps between stimuli as in trace conditioning [11]. A more specific role for the hippocampus in transfer of value was recently proposed using sensory preconditioning in humans [12, 13]. Unlike SOC, in sensory preconditioning, neutral stimuli are presented together prior to first-order conditioning. By this model, feedback-based

experiment 1a, discrimination of SOC stimuli by controls was most pronounced when higher barriers had to be crossed, requiring greater "confidence" [8]. In experiments 1b and 2, when only single SOs were paired with the CSs, rats with hippocampal lesions demonstrated equally shorter latencies for old compared with new stimuli, suggesting that they could discriminate between stimuli on the basis of familiarity, but not their specific valence (Table S3). Hippocampal functioning is associated with high-confidence accurate recollection, and extra-hippocampal structures are sufficient to support familiarity based memory, although the process underlying this pattern is debated [9, 10]. The dependence of high-confidence memory decisions on the hippocampus, as opposed to familiarity-based recognition that can be performed by extra-hippocampal structures, are here extended to SOC, a form of conditioning that can be considered paradigmatic of "non-declarative" learning [4, 5]. Importantly, our findings suggest that the hippocampus is needed not only for the acquisition of second-order associations, but also for their retention and expression as revealed by impaired performance following

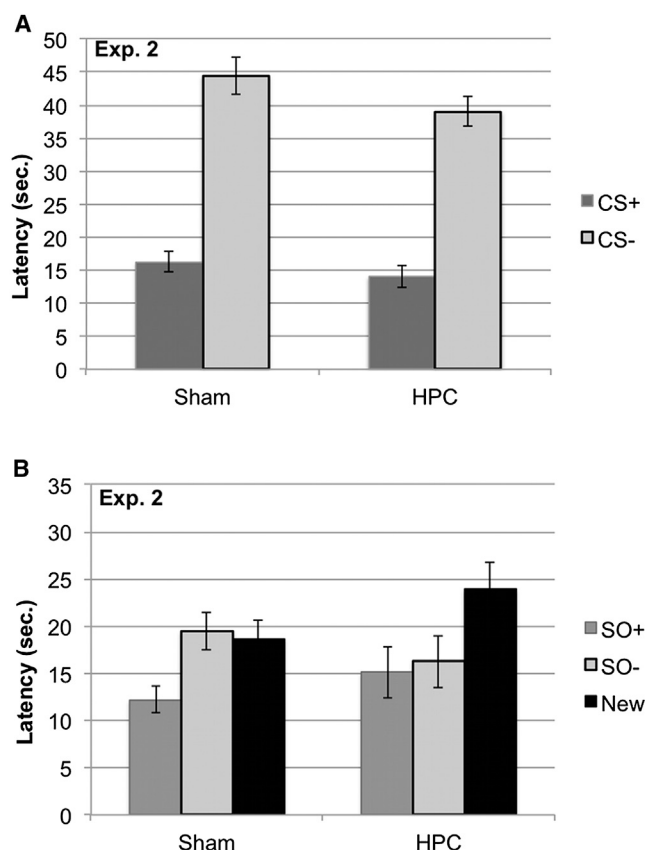


Figure 4. Response Latencies for Anterograde Stimuli in Experiment 2 (A) Latency to run for primary CS and (B) latency to run for SO and New stimuli. Error bars are SEM.

hippocampal lesions in the retrograde conditions of experiments 1a and 1b.

Recently, Lin and Honey [15] used a form of SOC to investigate the dynamics of memory decay. In contrast to our results, hippocampal damage led to slowed acquisition of auditory trace FOC when the interval between the stimulus and food reward was short (10 s), but not when it was long (40 s). Both lesioned and control groups exhibited stronger SOC to long-trace FOC stimuli than to short-trace FOC stimuli. There are numerous procedural differences between the two studies, but it is especially significant that Lin and Honey [15] used the same FOC stimulus as CS+ on some conditions and CS- on others, potentially leading also to SO valence overlap, whereas we had no overlap of stimuli across the different valences at all. Responding during SOC in the Lin and Honey [15] study could be performed based on the strength of hippocampal-independent familiarity processes. This would be similar to the familiarity effects observed in experiments 1b and 2 of the present research; however, in the absence of novel stimuli to compare SO learning to, that possibility remains to be clarified. Lin and Honey's results suggest that, under some conditions SOC may be able to withstand the effects of hippocampal lesions, but issues arising out of the procedural differences between the two studies warrant further investigation.

An important factor that might mediate the contribution of different nodes within the network of regions that mediate reinforcement learning is motivation. For example, sensory-

specific satiety differentially determines the contribution of orbitofrontal cortex during reinforcement learning (e.g., [16]). Motivation has also been shown to affect hippocampal contribution during contextual conditioning [17, 18], highlighting its potential relevance for SOC as well. In our experiments, rats were deprived during FOC, but not during SOC, and future experiments should determine whether the same hippocampal involvement occurs if rats are deprived during SOC. This might also explain the differences in results between the present study and Lin and Honey's [15], although it is not clear to what extent the rats in that study were deprived during SOC.

Complex chains of higher-order conditioned stimuli allow organisms to form models of action-outcome contingencies, knowledge that can be used to simulate prospective outcomes [19]. The demonstration that the hippocampus is important for the expression of SOC suggests its involvement not only in conscious, deliberate model-based planning, but also in automatic associative functions that support future choices and decisions. For example, humans with hippocampal lesions demonstrate impaired conscious future imagining [20] but normal gradients of temporal discounting of monetary values [21]. Neuroimaging studies also suggest no hippocampal involvement when money serves as a reinforcer [22, 23]. Our new perspective on the neurophysiology of appetitive conditioning could inform models of neuroeconomics in interpreting whether the incentive value of money and other material things we value results from primary or secondary conditioned associations. Finally, the findings could have a profound impact on our understanding of psychopathology—including eating disorders, depression, and substance abuse—that involve aberrant SOC [3]. For example, substance abuse is thought to involve the establishment of a multifarious network of CSs such that neutral stimuli become imbued with motivational value and serve as cues that trigger relapse following treatment. Our findings suggest that the hippocampal system, along with other structures (e.g., ventral striatum), could be a major player in this process. One counterintuitive consequence of this logic is that these associative networks might break down in amnesia, making relapse less likely (see [24] for a recent, related finding involving the underlying molecular mechanisms regulating this process in the amygdala).

To conclude, we found that unlike FOC, acquisition and retention of nondeclarative higher order conditioning is highly sensitive to hippocampal disruption. Our results indicate that neural structures that represent reward value and motivation [2, 3, 6, 7, 11, 19] cannot support, independently of the hippocampus, the representation of intrinsic relations between stimulus identity, reward value, and motivation when these relationships are of a higher order. Neurobiological models of conditioning need to address cognitive processes mediated by the hippocampus and its interaction with other structures such as sensory neocortical regions [25] when complex relational processing is required [26–28].

Experimental Procedures

Testing was conducted in a two-chamber (A and B) enclosure, separated by clear Plexiglas with a central opening. The experiments broadly consisted of five stages (see Supplemental Experimental Procedures and Figure 1 for details). These stages are described for experiment 1a and the changes made for experiments 1b and 2 are described below. (1) FOC. Water-deprived rats were trained to discriminate between two primary, first-order tones in chamber A: tone 1 (CS+) signaled water availability in chamber B, and tone 2 (CS-) signaled no water in chamber B. (2) SOC. Rats were taken off water deprivation and confined to chamber A where they learned

second-order associations by having each of the primary tones paired with five novel tones (i.e., CS+/SO+; CS−/SO−). (3) Inhibitory avoidance. Rats were confined to chamber B where they received mild foot shocks to deter indiscriminate running to the waterspout during test. Rats then received either neurotoxic hippocampal lesions or sham surgery. Postrecovery testing involved two stages: FOC and SOC testing. (4) FOC testing. Rats were placed back on water deprivation and discrimination of CS+/CS− was tested in the usual way to confirm intact FOC after hippocampal damage. (5) SOC testing. The rats remained on water deprivation. The previously presented secondary tones (5 SO+ and 5 SO−), as well as five New tones were presented in random order in chamber A. Following each tone presentation, rats were allowed up to 40 s to enter chamber B where water was always available. In experiment 1a, to enter chamber B, rats had to cross a barrier of variable height (0, 2, 4, 6, or 8 cm) to probe the animals' "confidence" level [8]. Crossing higher barriers presumably reflects higher confidence that the secondary tone is associated with reward. Models of hippocampal memory posit that higher-confidence memory is more strongly associated with hippocampal function (Supplemental Experimental Procedures; Figure S3) [9, 10].

The study was approved by Trent University Animal Care Committee and conducted in accordance with guidelines set by the Canadian Council on Animal Care.

Supplemental Information

Supplemental Information includes four figures, four tables, and Supplemental Experimental Procedures and can be found with this article online at <http://dx.doi.org/10.1016/j.cub.2014.07.078>.

Author Contributions

A.G., M.M., and G.W. designed the study. M.S. and G.W. conducted the experiments. A.G., M.M., M.S., and G.W. wrote the manuscript.

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